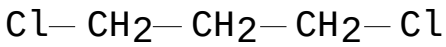
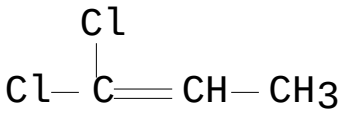
TOXICITY of Dichloropropanes and Dichloropropenes

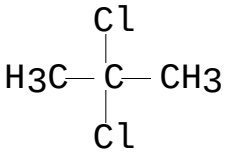
Structure of high priority CCL propanes and propenes under consideration for evaluation



1,3-Dichloropropane, $C_3H_6Cl_2$ CAS No.142-28-9, Molecular Wt. 112.9864



1,1-Dichloropropene, $C_3H_4Cl_2$ CAS No.563-58-6, Molecular Wt. 110.9706



2,2-Dichloropropane, $C_3H_6Cl_2$ CAS No.594-20-7, Molecular Wt. 112.9864

Nomination History

The EPA contaminant candidate list (CCL) for 1998 listed 1,3-dichlorpropane, 2,2-dichloropropane and 1,1-Dichloropropene for health effects research. These three chemicals were also listed under treatment research priorities. The EPA/AWWARF meeting in Virginia in 1999 reviewed the nearly 80 CCLs for prioritization for further research. These three chemicals, 1,3-dichloropropane, 2,2-dichloropropane, and 1,1-dichloropropene were among the approximately dozen chemicals that were considered to have the greatest public health concern research needs. Dr. Jeanette Wiltse, US EPA Office of Water in a May 18, 2000 memo also supports the consideration of 1,3-dichlorpropane, 2,2-dichloropropane and 1,1-Dichloropropene for further testing.

Occurrence

The EPA National Contaminant Occurrence Data of public water supplies shows that 1,3-dichloropropane was detected in 115 places of more than 30,000 sites analyzed. The same report shows that 2,2-dichloropropane was detected in 102 places. The analysis also shows that 1,1-dichloropropene was detected in 111 places of more than 30,000 sites. The average concentration of 1,3-dichloropropane was 765 µg/L. The same report shows that 2,2-dichloropropane was found at an average concentration of 0.3 µg/L with a maximum concentration of 6 µg/L. (Data from the EPA National Contaminant Occurrence Database, NCOD, 1992-1997). The average concentration of 1,1-dichloropropene was 777 µg/L. Analysis of river sediment from six sites in Japan failed to find these three chemicals and the sensitivity was 0.2 ng/g for 2,2-dichloropropane and 1,3-dichloropropane, and 0.1 ng/g for 1,1-dichloropropene (*1*). A table of occurrence of these three CCLs is also presented by Dr. Karin Wirth (US EPA) in this package.

Toxicity of <u>related</u> halopropanes and halopropenes

Most of the haloalkanes and haloalkenes are used as solvents and appear to have related mechanisms of toxicity (*2*). When given to rodents, many cause hepatotoxicity with renal toxicity found in fewer studies with exposure to haloalkanes and haloalkenes (*2*). Factors associated with increasing

toxicity include increasing number of halogens in the molecule and shorter carbon chain length. Decreasing toxicity associated with increasing chain length. The two carbon, 1,2-dichloroethane is considered carcinogenic in animals (*3*) while for 1,1,1,2-tetrachloroethane (*4*) and 1,1,2-trichloroethane (*5*) the evidence for carcinogenicity in animals is more limited. The three carbon propanes and propenes appear to be intermediate in toxicity, but only limited toxicity study data are available.

A review of the available toxicologic literature on halogenated propanes and propenes shows that of this class of chemicals, 1,3-dichloropropene (CAS 542-75-6) and 1,2-dichloropropane (CAS 78-87-5) are most widely used as agricultural nematicides, and therefore the subjects of toxicologic studies. A variety of genotoxic tests suggest that 1,3-dichloropropene and 1,2-dichloropane are mutagenic.

1,3 dichloropropene $Cl–CH_2–CH=CH–Cl$

In an inhalation study of 1,3-dichloropropene, B6C3F1 mice and F344 rats exposed up to 150 ppm 6 hours/day, 5 days/ week for13 weeks showed degeneration of the olfactory epithelium or a mild hyperplasia of the respiratory epithelium. The urinary bladder exhibited a diffuse hyperplasia of the transitional epithelium. The NOEL of 10 ppm was determined for rats and mice (*6*). When 1,3-dichloropropene was given in the diets at up to 100 mg/kg/day for rats and up to 175 mg/kg/day for mice for 13 weeks, the only treatment-related lesion was basal cell hyperplasia and hyperkeratosis in the non-glandular stomach of the rats. Treatment-related changes were not observed in the mice. NOAELs of 5 mg/kg/day and 15 mg/kg/day were determined for male rats and both sexes of mice; a NOAL of 5 mg/kg/day was determined for female rats.

Telone II (1,3-dichloropropene) was administered by corn oil gavage to rats (0, 25, 50 mg/kg) and mice (0, 50, and 100 mg/kg) three times/week for 104 weeks (*7*). Squamous cell papilloma of the forestomach (male/female rats; female mice), forestomach squamous cell carcinoma (male rats; female mice), transitional cell carcinoma of the urinary bladder (female mice), alveolar/bronchiolar adenoma (female mice), hepatic neoplastic nodules (male rats) were found (*7*). There is sufficient evidence for carcinogenicity of 1,3-dichloropropene for animals and this chemical is also considered a possible human carcinogen (*8*).

1,2 dichloropropane $Cl–CH_2–\underset{\displaystyle Cl}{\underset{|}{CH}}–CH_3$

No adverse effects were observed in mice exposed up to 681 mg/ m^3 of 1,2-dichloropropoene by inhalation for 13 weeks while rats exhibited only minimal toxicity to the nasal epithelium (*9*). Hepatocellular adenomas were seen in mice exposed up to 250 mg/kg/day of 1,2-dichloropropane by corn oil gavage for up to two years (*10*). An increase in mammary gland adenocarcinoma was observed in female rats exposed up to 250 mg/kg/day of 1,2-dichloropropane by corn oil gavage (*10*). Treatment-related effects were not observed male rats exposed to 125 mg/kg/day of 1,2-dichloropropane by corn oil gavage five times/week for up to two years (*10*). There is limited evidence for carcinogenicity of 1,3-dichloropropene in animals (*11*)

Toxicity of 1,3-dichloropropane, 2,2-dichloropropane and 1,1-dichloropropene

A. *In Vitro* Studies

In evaluation of a wide variety of alkanes for toxicity in lower species, increasing chlorine atoms at the C1 position resulted in greater toxicity. However, for algae, the effective concentration for 2,2-dichloropropane was 45 ppm compared to 221 ppm for 1,3-dichloropropane (*12*). When the 13 alkanes tested were ranked, 2,2-dichloropropane was the second most toxic with 1,3-dichloropropane ranked near the middle of the alkanes (*12*).

B. Animal Studies

Animal toxicology data were not found for the CCL high priority chemicals 1,3-dichloropropane, 1,1-dichloropropene or 2,2-dichloropropane.

C. Studies in Humans

Toxicity of 1,3-dichloropropane, 2,2-dichloropropane and 1,1-dichloropropene in humans has not been reported.

No studies in which the chemicals were administered in the drinking water were found. No data exist for 2,2-dichloropropane and 1,1-dichloropropene.

Rationale for consideration for evaluation of 1,3-dichloropropane, 2,2-dichloropropane, and 1,1-dichloropropene in NTP drinking water studies

All three chemicals, 1,3-dichloropropane, 2,2-dichloropropane, and 1,1-dichloropropene occur in the drinking water. These chemicals are structurally similar to 1,3-dichloropropene which is carcinogenic in animal studies and possible carcinogenic for humans (*8*). There is structural similarity to 1,3-dichloropropene that also shows limited evidence for carcinogenicity of for animals (*11*).

While all three chemicals occur infrequently and 2,2-dichloropropane often at low concentrations, there is essentially no information on these three chemicals. The toxicology studies must focus on mechanisms of toxicity that may be relevant at low concentrations. Based on studies of related propanes that have been studied, it is suggested that these chemicals are unlikely to be carcinogenic at low concentrations but quite probably carcinogenic if tested at higher concentrations. However, since they occur in the drinking water and are subject to regulation, short-term studies low concentration studies evaluating pathways that may be important in the carcinogenic process would be helpful to policy makers. The challenge for the toxicologists will be to design meaningful studies. It is proposed that the short-term studies be conducted at NHEERL with the National Toxicology Program providing chemistry and pathology support.

<u>Proposed Studies</u>

NHEERL Proposed Studies:

* Fourteen and 90-day studies of 2,2-dichloropropane, 1,3-dichloropropane, and 1,1-dichloropropene administered in the drinking water. Pharmacokinetic, metabolic, toxicologic, pathologic and mechanistic components should be part of the study design. NTP will collect and process tissues at EPA for standard 14-and 90 day studies.

* The chemicals should be evaluated for the ability to induce aberrant crypts in the colon and urinary bladder pathology (given the results from the 1,3-dichloropropene chronic study)

* The chemicals may be tested using the in vitro/in vivo human bladder carcinogenesis protocol

* Medaka studies may be considered, especially to look for low concentration effects.

It is recommended that these studies be designed and carried out in a coordinated, multidisciplinary manner and across divisions rather than through proposals submitted by individual investigators.

It is also recommended that NTP establish the stability and analytical procedures necessary to support the EPA studies at NHEERL.

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